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Af/ 1712

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HUESCHEN AND SAGE

Kathy E. Smith

Dated: September 17, 2003

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Applicant : Pascal LOMBARDIN, et al.

Serial No. : 09/743,248

Filed : March 6, 2001

Title : Thixotropic Formulations for Filling Hard Capsules

Art Unit : 1712

Examiner : Richard D. LOVERING, Esq.

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Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

RESPONSE AND AMENDMENT UNDER 37 CFR §§ 1.111 AND 1.115

Sir:

Responsive to the Office Action, **a Final Rejection**, dated June 19, 2003, kindly amend as follows:

IN THE CLAIMS: See Listing of Claims which will replace all prior versions of claims in the application.

R E M A R K S

The Applicants acknowledge the Examiner's Office Action of June 19, 2003 with appreciation. Claims 1,2, and 4-11 remain pending. The Office maintains rejections under 35 USC §§ 102(e), 103(a), and 112, second paragraph.

To begin, Claims 4, 5 and 7 are rejected under 35 USC § 112, second paragraph, for failing to claim with particularity.

It is the position of the Office that the language *'and more particularly'* in Claim 4 renders the claim indefinite. With this Response and Amendment, the applicants delete Claim 4 and incorporate its limitations into generic base Claim 1, thereby obviating the rejection.

The Office maintains its rejection of Claims 5 and 7 under 35 USC § 112, second paragraph, for indefiniteness asserting that the claim language does not involve proper "Markush" form. The applicants wish to point out that Claims 5 and 7 contain language of the form "wherein [X] is selected from 'A', 'B' and 'C'." USPTO support for this alternative claim language can be found in MPEP § 2173.05(h) which states that "alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims." The applicants submit that the phrases:

> *"wherein the dispersed phase is selected from hydrophilic or hydrophobic pyrogenic silica particles and ethylene oxide/propylene oxide copolymers"* (Claim 5)

and

> *"wherein the active substance is selected from milnacipran hydrochloride, baquimast, nifedipine ... paramethadone and griseofulvin"* (Claim 7)

is proper claim language according to USPTO procedure. Hence, the applicants respectfully solicit reconsideration and withdrawal of the 35 USC § 112, second paragraph, rejection of Claims 5 and 7.

Moving on, the Office maintains rejections of Claims 1, 2, 4-6, and 8-11, under 35 USC § 102(e) for anticipation, or in the alternative, under 35 USC § 103(a) for obviousness over Barnwell, et al. (USP 6,153,218). It is the position of the

Office that Barnwell, et al. disclose essentially the same compositions that the applicants disclose, which compositions are considered to "inherently" possess the same performance characteristics claimed by the applicants.

It is also the position of the Office that the applicants' Response of March 6, 2003 did not address the 102(e)/103 rejections based on Barnwell, et al. which were applied against Claim 3. Thus, the applicants' previous incorporation of the composition limitations of Claim 3 *(i.e., inclusion of a continuous dispersing phase, a dispersed phase, and at least one active ingredient)* into base Claim 1 was not found to effectively distinguish the rejected claims from the cited art.

With the instant Response, the applicants further distinguish the claimed composition from the disclosure of Barnwell, et al., by incorporating the limitations of Claim 4 *(i.e., the continuous phase consists of at least one vehicle selected from amphiphilic esters having a HLB between **3 and 15**)* into base Claim 1. The applicants submit that **Barnwell, et al., does not teach the use of amphiphilic esters having a HLB between 3 and 15 to obtain compositions with thixotropic properties, thereby allowing the filling of capsules at room temperature**. The applicants submit that the instant Amendment literally distinguishes all claims from the cited art.

Moreover, considering the Office rejection on a point-by-point basis, we begin by noting that the Office asserts that the combination of Aerosil, Gelucire 44/14 and propanolol disclosed at Barnwell, et al. Example 1 anticipates the claimed thixotropic composition. The applicants note that the formulation of Example 1 consists of two phases (i.e., a rapid-release phase and a sustained-release phase) that are separated by a physical barrier of Gelucire 44/14. Aerosil and propanol are part of the sustained-release phase which is distinct from the

barrier phase of Gelucire 44/14. The applicants emphasize that the Gelucire 44/14 is not dispersed within the sustained-release phase of the formulation. Gelucire 50/02 is included in the sustained-release phase of Barnwells' composition; however, the glyceride has a HLB of 2, does not possess the instant essential performance characteristics, and therefore does not anticipate the composition of Claim 1 as instantly amended. Thus, the Office basis for anticipation is no longer made.

It is important to understand what Barnwell, et al. teach. Barnwell, et al. disclose a capsule, which contains two (2) distinct phases: a rapid-release phase and a sustained-release phase. Barnwell, et al. also teach the use of Gelucire to either form a solid physical **barrier** between the two phases, or to **solidify a liquid phase** of the composition. Barnwell, et al. exemplify two types of biphasic compositions. According to one variant, the rapid-release phase is liquid, the sustained-release phase is solid, and the two phases are separated by a solid physical barrier made of Gelucire, a glyceride. This physical barrier is intended to prevent the two phases from mixing (see Example 1). The instant invention cannot read on this dosage form with physical/mechanical separation between the two phases. According to a second variant, there is no physical/mechanical barrier between the two phases. The rapid-release phase is formulated as a solid, rather than a liquid, to prevent intermixing with the solid sustained-release phase. This is achieved by mixing Gelucire 33/01 with the rapid-release phase components (see Col. 4, lines 11-22 and Example 3) to render the phase solid. Consequently, both phases of this second variant must be hot-filled. Therefore, the physical characteristics of the instant dosage form cannot read on this second Barnwell, et al. variant because the applicants neither claim solid, hot-filled phases, nor is there any disclosed advantage to develop such a formulation.

In both variants, Barnwell, et al., disclose **solid phases which must be molten prior to filling the capsules under hot temperature**. The preparation comprises the **melting of Gelucire** (Col. 5, lines 32-35). **The capsules are filled under hot temperature; not under room temperature as the instant claimed composition. Once the capsules are filled, the composition solidifies upon cooling** (see Example 1, Col. 5, lines 29-30 or lines 34-35 and Example 3, Col. 7, lines 22-23). Barnwell, et al. do not disclose compositions having the instant advantageous **thixotropic** properties. The Office has provided no motivation to advance the formulation art to the point which the applicants have. Rather, the Office employs improper hindsight reasoning to conclude that the instant invention is obvious from the inferior dosage form disclosed in the prior art.

The significance of the instant invention derives from the rheological properties of the instant claimed **thixotropic** composition which ensures effective filling at **room temperature** and the **absence of leaks** from the filled hard capsules which are incident to the hot-filling of the prior art (Specification, page 4, lines 5-8).

The instant Specification explains on page 4, lines 9-17 that a *"liquid or pasty thixotropic composition has a shear-thinning character which is manifested by a reduction in the apparent viscosity under the effect of increasing shear. Furthermore, any variation in the shear conditions causes a structural modification delayed over time. Thus, in particular, a gradual, total or partial recovery in consistency is observed after the shear has stopped."*

The compositions according to the instant invention are therefore defined, on one hand, by their shear-thinning nature (i.e., their viscosity decreases when the intensity of the shear increases), and, on the other hand, by the decrease in their viscosity over time for a given shear (Specification, page 5, lines 20-25).

The Applicants reemphasize that the claimed compositions are **liquid or pasty at room temperature**, thereby allowing easy filling of capsules at **room temperature**. This is supported by the Example on page 10 of the instant Specification wherein, the process of preparation of the composition does not comprise a melting step. **There is no melting step because the compositions are dispersions containing a continuous dispersing phase (which is liquid) and a dispersed phase.** Such **critical limitations** are claimed. Moreover, and in contrast, the absence of such critical limitations is thoroughly disclosed in the cited art, which speaks to the necessity of hot-filling. Such completely distinct performance characteristics distinguish the instant invention. Moreover, the Office has failed to demonstrate that those skilled in the art would have comprehended the instant invention from the cited art. Rather, the instant invention represents the essence of invention, namely identifying a new dosage form which meets needs not heretofore recognized, but when identified acknowledged for its significance.

Thus, the applicants submit that in view of the differences in the physical properties between the claimed composition and that of Barnwell, et al. the instant composition is neither anticipated nor made obvious by the disclosure of the cited art.

Finally, the Office maintains the rejection of Claim 7 for obviousness under 35 USC § 103(a) based on the disclosure of Barnwell, et al., in view of Crison, et al. The Office asserts that since both references disclose formulations for increasing the bioavailability of poorly water-soluble drugs, their teaching may be combined by one skilled in the art to make obvious the instant claims specifically claiming a nifedipine formulation. That is, it would have been obvious to one skilled in the art, at the time the applicants' invention was made,

to use nifedipine of Crison, et al., instead of propranolol in the composition of Barnwell, et al. to achieve the same composition as that claimed by the applicants.

Crison, et al. disclose a composition for enhancing the bioavailability of an active substance comprising an emulsion which contains an oil (or another lipidic material), a surfactant and a hydrophobic co-surfactant (Col. 3, lines 38-46). However, the preparation of the capsules implicitly comprises filling under **hot temperatures**, as it is stated that the emulsion is allowed to cool (Col. 4, lines 65-67).

The applicants assert that the disclosure of Barnwell, et al. is irrelevant to the patentability of the instant composition, and thus, submit that the obviousness rejection based on the combination of Barnwell,et al. in view of Crison, et al. is rendered moot.

Reconsideration and withdrawal of the rejections under 35 USC §§ 102(e) and 103(a) are respectfully solicited.

* * * * *

Accordingly, entry of the present amendment, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned attorney has made an earnest effort to place this application into condition for immediate allowance. If he can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call him at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,
THE FIRM OF HUESCHEN AND SAGE

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Enclosure: Listing of Claims, Postal Card Receipt

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LISTING OF CLAIMS

1. (presently amended) Liquid or pasty thixotropic compositions which contain a continuous dispersing phase, a dispersed phase and one or more active substances, intended for filling hard capsules at room temperature, wherein :

   - their complex modulus G* is greater than about 100 Pa,
   - their phase shift δ is less than about 45°,
   - their viscosity decreases with increasing shear rate,
   - under the effect of a constant shear rate γ_o, the viscosity of the said compositions decreases in a delayed manner over time and stabilizes at the equilibrium value η_{eq} of between 10 mPa.s and about 10,000 mPa.s, when γ_o is between 100 and 1000 s^{-1} and
   - after making the said shear rate 0, the complex modulus and the phase shift of the said compositions resume, after a time t of less than 1 hour, G* and δ values of greater than about 100 Pa and of less than about 45°, respectively.

   and wherein the continuous phase consists of at least one vehicle selected from amphiphilic esters having an HLB between 3 and 15.

2. (previously presented) A composition according to Claim 1, wherein:
   - G* is greater than 1000 Pa, and/or
   - δ is less than 25° and /or
   - η_{eq} is between 100 and 1500 mPa.s when γ_o is between 100 and 1000 s^{-1} and/or
   - t is less than 30 min.

3. (previously deleted)

4. (presently deleted) ~~A composition according to Claim 1, wherein the continuous phase consists of at least one vehicle selected from amphiphilic esters having an HLB of between 3 and 15 and more particularly polyglycolized glycerides.~~

5. (previously presented) A composition according to Claim 1, wherein the dispersed phase is selected from hydrophilic or hydrophobic pyrogenic silica particles and ethylene oxide/propylene oxide copolymers, the latter making it possible to achieve, when combined with the continuous phase, HLB values ranging up to about 20.

6. (previously presented) A composition according to Claim 1, wherein the active substance is liquid, pasty or solid.

7. (previously presented) A composition according to Claim 6, wherein the active substance is selected from milnacipran hydrochloride, baquimast, nifedipine, triamterene, aluminum hydroxychloride, sodium salicylate, vancomycin, paramethadone and griseofulvin.

8. (previously presented) A composition according to Claim 1, wherein the dispersed phase of the preparations according to the invention represent 1 to 30% m/m of the preparation.

9. (previously presented) A composition according to Claim 8, wherein the dispersed phase of the dispersions according to the invention represent from 5 to 15% m/m of the preparation.

10. (previously presented) A composition according to Claim 1, wherein the hard capsules consist of gelatin or of any cellulose polymer capable of fulfilling the functions of the use of gelatin in the form of a hard capsule.

11. (previously presented) A composition according to Claim 1, wherein the hard capsules consist of hydroxypropylmethylcellulose.